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(54) Title: METHOD FOR PREVENTING OR TREATING PAIN BY ADMINISTERING AN ENDOTHELIN ANTAGONIST

(57) Abstract: Prevention or treatment of pain by administration of an endothelin antagonist.

5 **METHOD FOR PREVENTING OR TREATING PAIN BY ADMINISTERING
AN ENDOTHELIN ANTAGONIST**

 This application claims priority to U.S. Provisional Application Serial No.
60/257,840 filed December 21, 2000, the entirety of which is incorporated herein by
10 reference.

Field of the Invention

 The present invention relates to the prevention or treatment of pain by
administering an endothelin antagonist to a subject in need thereof.

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Brief Description of the Invention

 Endothelin-1 (ET-1) is a polypeptide with very potent vasoconstrictor activity.
Elevated levels ET-1 are found in a variety of diseases including advanced prostate
20 cancer and localized prostate cancer. It has been discovered that ET-1 not only
functions as a vasoconstrictor but that it also has other functions, serving, for instance,
as a growth factor alone or in combination with other hormones and peptides, as in
prostate cancer (see, e.g., *Nature Med.* 1, 944-949, (1995)). In addition, as disclosed
in WO 98/46076, ET-1 is related to the sorafotoxins, which are painful and lethal
25 moieties in the venom of certain snakes of the genus *Atractapsis*. Similar to venom in
a snake bite, recombinant ET-1 has been reported to produce intense pain in humans
after the localized injection of high concentrations. Thus, for instance, in prostate
cancer, a high localized concentration of ET-1 produced by the cancer cells is likely to
be a major contributor to the high degree of pain associated with the late stage of the
30 disease. Accordingly, molecules that prevent or inhibit the production of ET-1 can be
expected to be useful to prevent and treat pain associated with elevated levels of
endothelin.

 Endothelin antagonists, which are compounds capable, *inter alia*, of inhibiting
the binding of endothelin peptides to endothelin receptors, are useful in the treatment
35 of endothelin-related disorders. While certain such compounds have been described
as having utility in the treatment of hypertension, the present invention provides a
method employing these compounds specifically for the treatment of pain.

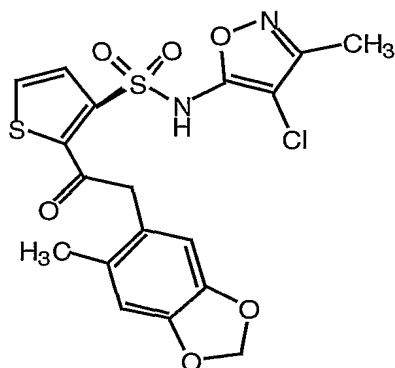
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Detailed Description of the Invention

The present invention provides a method for the prevention or treatment of pain associated with elevated levels of endothelin in a mammal, comprising administering an endothelin antagonist to said mammal in an amount effective therefor.

The endothelin antagonist employed may be any compound capable of inhibiting the action of endothelin peptides, especially, endothelin-1 (ET-1), endothelin-2 (ET-2) and/or endothelin-3 (ET-3). The endothelin antagonists described in the following documents, incorporated herein by reference in their entirety, are exemplary of those contemplated for use in the present method: U.S. Patent No. 5,378,715; U.S. Patent No. 5,514,696; U.S. Patent No. 5,420,123; U.S. Application Serial No. 114,251, filed August 30, 1993; U.S. Application Serial No. 08/728,238, filed October 8, 1996; European Patent Application 702,012; U.S. Application Serial No. 08/754,715, filed November 21, 1996; U.S. Application Serial No. 08/692,869, filed July 25, 1996; U.S. Application Serial No. 60/011,974, filed February 20, 1996; U.S. Application Serial No. 60/013,491, filed March 12, 1996; U.S. Application Serial No. 60/015,072, filed April 9, 1996; World Patent Application 94/27979; U.S. Patent No. 5,543,521; U.S. Patent No. 5,464,853; U.S. Patent No. 5,514,691; WO 96/06095; WO 95/08550; WO 95/26716; WO 96/11914; WO 95/26360; EP 601386; EP 633259; US 5,292,740; EP 510526; EP 526708; WO 93/25580; WO 93/23404; WO 96/04905; WO 94/21259; GB 2276383; WO 95/03044; EP 617001; US 5,334,598; WO 95/03295; GB 2275926; WO 95/08989; GB 2266890; EP 496452; WO 94/21590; WO 94/21259; GB 2277446; WO 95/13262; WO 96/12706; WO 94/24084; WO 94/25013; U.S. 5,571,821; WO 95/04534; WO 95/04530; WO 94/02474; WO 94/14434; WO 96/07653; WO 93/08799; WO 95/05376; WO 95/12611; DE 4341663; WO 95/15963; WO 95/15944; EP 658548; EP 555537; WO 95/05374; WO 95/05372; US 5,389,620; EP 628569; JP 6256261; WO 94/03483; EP 552417; WO 93/21219; EP 436189; WO 96/11927; JP 6122625; JP 7330622; WO 96/23773; WO 96/33170; WO 96/15109; WO 96/33190; US 5,541,186; WO 96/19459; WO 96/19455; EP 713875; WO 95/26360; WO 96/20177; JP 7133254;

- 5 WO 96/08486; WO 96/09818; WO 96/08487; WO 96/04905; EP 733626;
WO 96/22978; WO 96/08483; JP 8059635; JP 7316188; WO 95/33748;
WO 96/30358; US 5,559,105; WO 95/35107; JP 7258098; US 5,482,960; EP 682016;
GB 2295616; WO 95/26957; WO 95/33752; EP 743307; and WO 96/31492; such as
the following compounds described in the recited documents: BQ-123 (Ihara, M., et
10 al., "Biological Profiles of Highly Potent Novel Endothelin Antagonists Selective for
the ET_A Receptor", *Life Sciences*, Vol. 50(4), pp. 247-255 (1992)); PD 156707
(Reynolds, E., et al., "Pharmacological Characterization of PD 156707, an Orally
Active ET_A Receptor Antagonist", *The Journal of Pharmacology and Experimental
Therapeutics*, Vol. 273(3), pp. 1410-1417 (1995)); L-754,142 (Williams, D. L., et al.,
15 "Pharmacology of L-754,142, a Highly Potent, Orally Active, Nonpeptidyl Endothelin
Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol.
275(3), pp. 1518-1526 (1995)); SB 209670 (Ohlstein, E. H., et al., "SB 209670, a
rationally designed potent nonpeptide endothelin receptor antagonist", *Proc. Natl.
Acad. Sci. USA*, Vol. 91, pp. 8052-8056 (1994)); SB 217242 (Ohlstein, E. H., et al.,
20 "Nonpeptide Endothelin Receptor Antagonists. VI: Pharmacological Characterization
of SB 217242, A Potent and Highly Bioavailable Endothelin Receptor Antagonist",
The Journal of Pharmacology and Experimental Therapeutics, Vol. 276(2), pp. 609-
615 (1996)); A-127722 (Opgenorth, T. J., et al., "Pharmacological Characterization
of A-127722: An Orally Active and Highly Potent ET_A-Selective Receptor
25 Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol.
276(2), pp. 473-481 (1996)); TAK-044 (Masuda, Y., et al., "Receptor Binding and
Antagonist Properties of a Novel Endothelin Receptor Antagonist, TAK-044
{ Cyclo[D- α -Aspartyl-3-[(4-Phenylpiperazin-1-yl)Carbonyl]-L-Alanyl-L- α -Aspartyl-
D-2-(2-Thienyl)Glycyl-L-Leucyl-D-Tryptophyl]Disodium Salt}, in Human
30 Endothelin_A and Endothelin_B Receptors", *The Journal of Pharmacology and
Experimental Therapeutics*, Vol. 279(2), pp. 675-685 (1996)); bosentan (Ro 47-0203,
Clozel, M., et al., "Pharmacological Characterization of Bosentan, A New Potent
Orally Active Nonpeptide Endothelin Receptor Antagonist", *The Journal of
Pharmacology and Experimental Therapeutics*, Vol. 270(1), pp. 228-235 (1994)); and
35 TBC-11251, i.e.:



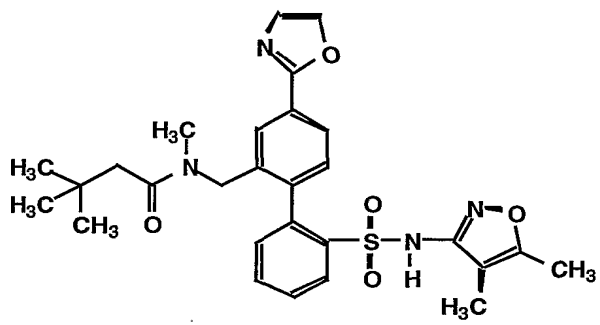
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(IBC International Conference on Endothelin Inhibitors, Coronado, CA (Feb 1996) and 211th American Chemical Society National Meeting, New Orleans, LA (March 1996)). These exemplary compounds may, for example, be prepared by methods, and employed at dosages, such as those described in the aforementioned documents.

10 Endothelin antagonists containing a sulfonamide moiety (-SO₂-NH-) are preferred, particularly those described in U.S. Patent No. 5,612,359. and U.S. Patent No. 6,043,265. Especially is the following compound:

N-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)][1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide, having the structure:

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and pharmaceutically acceptable salts thereof. These preferred endothelin antagonists, and particularly the especially preferred compound shown above, are described as having a number of utilities such as the treatment of congestive heart failure and hypertension (see e.g., the disclosures in U.S. Patent No. 5,612,359 and U.S. Application Serial No. 60/035,832,) wherein the complete recitation of all these utilities is incorporated herein by reference; these preferred endothelin antagonists may be employed for each of these utilities alone or in combination with an agent

5 such as an angiotensin II (AII) receptor antagonist (including irbesartan, 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one).

The mammal may be any mammal subject to this malady, especially, a human. The endothelin antagonist may be administered in any suitable manner such as orally or parenterally, in an effective amount, such as within a dosage range of about 0.1 to
10 about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) in single or 2 to 4 divided daily doses.

The present invention also provides pharmaceutical compositions for the prevention or treatment of pain, comprising an endothelin antagonist in an amount
15 effective therefor and a pharmaceutically acceptable vehicle or diluent. The endothelin antagonist can be utilized in a composition such as tablet, capsule, sterile solution or suspension, compounded in a conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc. as called for by accepted pharmaceutical practice.

20 In the methods and compositions of the present invention, the endothelin antagonist may, for example, be employed alone, in combination with one or more other endothelin antagonists, or with another compound or therapies useful for the treatment of pain associated with elevated levels of endothelin, such as narcotics. Additionally, the compounds of the present invention may be employed in
25 combination with typical therapies used in the treatment of cancer, such as radiation therapy, estramustine, CDK inhibitors, antiangiogenic agents (such as MMPI), monoclonal antibodies (such as Herceptin and anti-EGF receptor), 17beta-HSD3 inhibitor, adrenal inhibition (e.g., aminoglutethimide, or ketoconazole), or proapoptic agents (such as retinoids). Additionally, the endothelin antagonists of the present
30 invention may be employed in combination with one or more other compounds useful in the treatment of endothelin-associated disorders. For example, the compounds of this invention can be formulated in combination with endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists such as ifetroban; potassium channel openers; thrombin inhibitors (e.g., hirudin and the like);
35 growth factor inhibitors such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents such as GPIIb/IIIa blockers (e.g.,

5 abciximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants such as warfarin, low molecular weight heparins such as enoxaparin, Factor VIIa inhibitors, and Factor Xa inhibitors such as those described in U.S. Serial No. 09/496,571 filed February 2, 2000 (attorney docket HA 723); renin inhibitors; angiotensin converting enzyme (ACE) inhibitors
10 such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, lisinopril and salts of such compounds; neutral endopeptidase (NEP) inhibitors; vasopectidase inhibitors (dual NEP-ACE inhibitors) such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or
15 nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants such as questran; niacin; anti-atherosclerotic agents such as ACAT inhibitors; MTP inhibitors such as those described in U.S. Serial No. 09/007,938 filed January 16, 1998 (attorney docket HX 91); calcium channel blockers such as amlodipine besylate; potassium
20 channel activators; alpha-adrenergic agents, beta-adrenergic agents such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide or benzothiazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide,
25 triamterene, amiloride and spironolactone and salts of such compounds; thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase and anisoylated plasminogen streptokinase activator complex (APSAC); anti-diabetic agents such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas
30 (e.g., glimepiride, glyburide, and glipizide), biguanide/glyburide combinations such as those described in U.S. Serial No. 09/432,465 filed November 3, 1999 (attorney docket LA 46) and U.S. Serial No. 09/460,920 filed December 14, 1999 (attorney docket LA 46a); thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists such as
35 spironolactone and eplerenone; growth hormone secretagogues such as those described in U.S. Serial No. 09/417,180 filed October 12, 1999 (attorney docket LA

5 25) and U.S. Serial No. 09/506,749 filed February 18, 2000 (attorney docket LA 26);
aP2 inhibitors such as those described in U.S. Serial No. 09/391,053 filed September
7, 1999 (attorney docket LA 24a) and U.S. Serial No. 09/390,275 filed September 7,
1999 (attorney docket LA 24b); digitalis; ouabian; non-steroidal antiinflammatory
10 drugs (NSAIDS) such as aspirin and ibuprofen; phosphodiesterase inhibitors such as
PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., sildenafil); protein
tyrosine kinase inhibitors; antiinflammatories; antiproliferatives such as methotrexate,
FK506 (tacrolimus, Prograf), mycophenolate and mofetil; chemotherapeutic agents;
immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents,
15 such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and
triazenes); antimetabolites such as folate antagonists, purine analogues, and
pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin,
dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein
transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone),
20 estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing
hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor
agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing
agents such as paclitaxel (Taxol®), docetaxel (Taxotere®), and epothilones A-F or
their analogs or derivatives; plant-derived products, such as vinca alkaloids,
epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase
25 inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane,
hexamethylmelamine, platinum coordination complexes such as cisplatin and
carboplatin); cyclosporins; steroids such as prednisone or dexamethasone; gold
compounds; cytotoxic drugs such as azathioprine and cyclophosphamide; TNF-alpha
inhibitors such as tenidap; anti-TNF antibodies or soluble TNF receptor such as
30 etanercept (Enbrel) rapamycin (sirolimus or Rapamune), leflunimide (Arava); and
cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib
(Vioxx).

The effective amount of a compound of the present invention may be
determined by one of ordinary skill in the art, and includes exemplary dosage amounts
35 for a human of from about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50
mg/kg and more preferably from about 0.5 to about 25 mg/kg of body weight (or from

5 about 1 to about 2500 mg, preferably from about 5 to about 500 mg) of active
compound per day, which may be administered in a single dose or in the form of
individual divided doses, such as from 1 to 4 times per day. It will be understood that
the specific dose level and frequency of dosage for any particular subject may be
varied and will depend upon a variety of factors including the activity of the specific
10 compound employed, the metabolic stability and length of action of that compound,
the species, age, body weight, general health, sex and diet of the subject, the mode and
time of administration, rate of excretion, drug combination, and severity of the
particular condition. Preferred subjects for treatment include animals, most preferably
mammalian species such as humans, and domestic animals such as dogs, cats and the
15 like, subject to endothelin-dependent disorders.

The above other therapeutic agents, when employed in combination with the
compounds of the present invention, may be used, for example, in those amounts
indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one
of ordinary skill in the art.

20 The present invention also provides pharmaceutical compositions comprising
at least one of the compounds of the formula I capable of treating an endothelin-
dependent disorder in an amount effective therefor, and a pharmaceutically acceptable
vehicle or diluent. The compositions of the present invention may contain other
therapeutic agents as described below, and may be formulated, for example, by
25 employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical
additives of a type appropriate to the mode of desired administration (for example,
excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques
such as those well known in the art of pharmaceutical formulation or called for by
accepted pharmaceutical practice.

30 The compounds of the formula I may be administered by any suitable means,
for example, orally, such as in the form of tablets, capsules, granules or powders;
sublingually; buccally; parenterally, such as by subcutaneous, intravenous,
intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile
injectable aqueous or non-aqueous solutions or suspensions); nasally such as by
35 inhalation spray; topically, such as in the form of a cream or ointment; or rectally such
as in the form of suppositories; in dosage unit formulations containing non-toxic,

5 pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or
10 osmotic pumps. The present compounds may also be administered liposomally. For example, the active substance can be utilized in a composition such as tablet, capsule, solution or suspension containing about 5 to about 500 mg per unit dosage of a compound or mixture of compounds of formula I or in topical form for wound healing (0.01 to 5% by weight compound of formula I, 1 to 5 treatments per day). They may
15 be compounded in a conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., or with a topical carrier. The compounds of formula I can also be formulated in compositions such as sterile solutions or suspensions for parenteral administration. About 0.1 to 500 milligrams of a compound of formula I may be compounded with a physiologically acceptable
20 vehicle, carrier, excipient, binder, preservative, stabilizer, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is preferably such that a suitable dosage in the range indicated is obtained.

Exemplary compositions for oral administration include suspensions which
25 may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders,
30 extenders, disintegrants, diluents and lubricants such as those known in the art. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight
35 excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy

5 propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

10 Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable
15 solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

20 Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier
25 such as Plastibase (mineral oil gelled with polyethylene). For example, the compounds of the invention may be administered topically to treat peripheral vascular diseases and as such may be formulated as a cream or ointment.

5

What is claimed is:

1. A method for preventing or treating pain in a mammal, comprising administering to said mammal the compound N-[[2'-[[4,5-dimethyl-3-
10 isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide or a salt thereof in an amount effective therefor.
2. The method of claim 1, wherein said mammal is a human.
- 15 3. The method of claim 1 wherein said pain is the pain associated with prostate cancer.
4. A pharmaceutical composition for the prevention or treatment of pain in a mammal, comprising the compound N-[[2'-[[4,5-dimethyl-3-
20 isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide or a salt thereof in an amount effective therefore and a pharmaceutically acceptable vehicle or diluent optionally in combination with at least one narcotic.

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(88) Date of publication of the international search report:
8 May 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR PREVENTING OR TREATING PAIN BY ADMINISTERING AN ENDOTHELIN ANTAGONIST

(57) Abstract: Prevention or treatment of pain (especially pain associated with prostate cancer) by administration of an endothelin antagonist, more particularly of N-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl]-4-(2-oxazolyl)[1,1'-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide or a salt thereof, optionally in combination with a narcotic.



WO 02/049630 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/50781

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/422 A61P29/02 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBASE, BIOSIS, PHARMAPROJECTS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 33780 A (SQUIBB BRISTOL MYERS CO) 6 August 1998 (1998-08-06) cited in the application	1,2,4
Y	abstract example 2 page 8 lines 8,14,24 & US 6 043 265 A 28 March 2000 (2000-03-28) ---	3
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 September 2002

Date of mailing of the international search report

18/09/2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/50781

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NELSON J B ET AL: "The role of endothelin-1 and endothelin receptor antagonists in prostate cancer." BJU INTERNATIONAL. ENGLAND APR 2000, vol. 85 Suppl 2, April 2000 (2000-04), pages 45-48, XP008007943 ISSN: 1464-4096 the whole document, especially page 46 right column and page 47 left column ---	3
Y	DAVAR G ET AL: "Behavioral signs of acute pain produced by application of endothelin-1 to rat sciatic nerve." NEUROREPORT. ENGLAND 13 JUL 1998, vol. 9, no. 10, 13 July 1998 (1998-07-13), pages 2279-2283, XP008007945 ISSN: 0959-4965 page 2282 ---	3
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P,X	WO 01 91736 A (WARNER LAMBERT CO ;DOOLEY DAVID JAMES (US)) 6 December 2001 (2001-12-06) abstract page 2, line 16 page 3, line 3 page 5, line 22 page 12, line 1 - line 9 page 32, line 1 - line 2 page 44, line 26 - line 31 page 45, line 1 - line 14 page 63, line 21 - line 32 page 64, line 1 - line 7 -----	1,2,4
A		3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/50781

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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